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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,217	05/06/2002	Peter Francis Leadlay	0380-P02746US0	9951

110 7590 11/14/2005

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,217	LEADLAY ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,10-45,48 and 4912* is/are pending in the application.

4a) Of the above claim(s) *13-29,35,36 and 39-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 5, 7, 10-12, 30-34, 37, 38, and 49* is/are rejected.

7)☒ Claim(s) *2,3,8 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

The application has been amended as requested in the communication filed August 22, 2005. Accordingly, claims 1-5, 7, 8, 10-12, and 30-34 have been amended, and claims 6, 9, 46, and 47 have been canceled. Claims 13-29 and 35-45 remain withdrawn from further examination as they are drawn to non-elected subject matter.

Claims 1-5, 7, 8, 10-12, 30-34, 37, 38, 48, and 49 are under consideration in this Office action.

The amendment filed May 6, 2002 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. This application is a national stage application of PCT/GB00/02072 filed May 30, 2001. As such, the instant application should be identical to the PCT/GB00/02072 as filed and should include only the nucleic and amino acid sequences found in the international application. The new sequence listing filed May 6, 2002 contains new SEQ ID NO's: 1-4 (about 30000 bp each), which are not part of the original application. The new sequences are fragments of the originally filed 103,551 bp SEQ ID NO: 1. New SEQ ID NO's: 1-4 are considered new matter and add considerable confusion in the interpretation of the results in Table 1. Applicants must remove the new matter from the sequence listing. A new paper copy and computer readable form (CRF) of sequence listing the original 103,551 bp of SEQ ID NO: 1, followed by the amino acid sequences and the various nucleic acid primers and probes in the application. Newly filed SEQ ID NO's: 1-4 on May 6, 2002, which is not supported by the original disclosure must be deleted.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Objection:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). Specifically, rule 37 CFR 1.821 (d) states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Clearly, neither the specification nor the claims are in compliance with rule 37 CFR 1.821(d). For example, SEQ ID NO: 22 should follow MonAIV in claim 1, and the appropriate segment of nucleic acid of SEQ ID NO: X should be inserted following the

various genes in claim 4. Table I describes the activities encoded by the gene cluster of residues number 1-103,450, but the specification or the sequence listing does not contain a nucleic acid sequence containing >100,000 bp. It appears that the numbers in the Table correspond to a hypothetical sequence composed of SEQ ID NO's: 1-4. Applicants are advised to introduce SEQ ID NO: X which is the combination of SEQ ID NO's: 1-4 in the correct order. Perfecting compliance with the sequence rules is required.

Because of the extensive amendment required for perfecting the sequence rules, applicants are advised to file a new specification containing all amendment filed previously and the required amendment to perfect the compliance with the sequence rules, annotated copy of the specification indicating the addition and deletion, and a statement indicating that the amended specification contains no new matter.

The disclosure is objected to because of the following informalities: The specification should be consistent in the reference to the protein and the nucleic acid in the application. For example "monAIV" and "MonAIV" are both used in the specification and amendment to mean the same thing, i,e, the polypeptide of SEQ ID NO: 22. Similarly, applicant should pick one and write it in italic to refer to the gene. Applicants should pick one and use it through out the specification.

Appropriate correction is required.

New Objection:

The drawings are objected to because Figure 1 is confusing and not clear. There is no R shown in the structure presented in Figure 1. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement-drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 is dependent on

claim 3, which is limited monAIV to SEQ ID NO: 22. Claim 4 expands the scope of claim 3 to include at least one or more of other open reading frames from the gene cluster.

Claim 1 and 3 are objected to because of the following informalities: "MonAIV" should be ----monAIV-----. Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 4, 5, 7, 8, 10-12, 30-34, 37, 38, 48, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claim 1, 4, 30, and 34 are not in compliance with the sequence rule, and therefore, is considered indefinite, see above.

(b) Claim 8 is confusing and indefinite because there is no nucleic acid sequence containing >103,000 bp and, thus, all the activities listed in Table I, see he discussion above. None of the nucleic acid sequences of SEQ ID NO's: 1-4 contains the numerical residues as listed in Table 1. As indicated above and below current SEQ ID NO: 1-4 represent new matter in the application. Applicants may overcome this rejection by reintroducing original SEQ ID NO: 1 to the application.

(c) Items (a)-(g) renders claims 1 renders the claim indefinite becuase the resulting claim does not set forth the metes and bound of the claimed invention. The claimed amino acid fragments (a)-(g) in claim 1 are not defined by the specification or the claims, and one of ordinary skill in the art would not know what they are. The claim may be amended to say the poleypetide encoded by residues X-Y of original SEQ ID NO: 1.

(c) The phrases "not naturally associated thereto" in claims 30-34, and "naturally received" in claim 33 render the claims indefinite because the resulting claims do not set fourth the metes and bound of the claimed invention. First, the specification does not teach one of ordinary skill in the art how to distinguish a naturally occurring from a man-made module or domain associated with monAIV. Second, the word "associated" in the context of the claim is not clear and has more than one meaning. It could mean that it is not naturally associated on the same polypeptide, i.e., monAIV polypeptide. In contrast, it is known in the prior art that polyketide

synthases from the same gene clusters are non-covalently associated with one another. In another word, all catalytic domains, modules, and open reading frame in a gene cluster are associated with one another. Since one of ordinary skill in the art would not know which meaning the applicant intended to mean and the specification does not shed a light on what the applicants want to claim, the claims are found indefinite and confusing. Regarding claim 33, it is well known in the art that the starter unit can vary and many polyketide synthases accept other acyl groups from those originally thought to be "naturally received". The specification does not teach all possible "naturally received" acyl groups, and one of ordinary skill in the art would not know. Thus, the claim is considered indefinite and confusing. Claims 30-34 are generally narrative in nature and are not consistent with U. S. practice.

(d) The word "from" in claim 49, line 2 renders the claim indefinite and confusing. For examination purposes only, the word "from" is deleted.

(e) Claims 5, 7, 10-12, 37 and 38 are included in this ejection because they are dependent on a rejected claim and do not cure its deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 10-12, 30-34, 37, 38, and 48 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Also, the amendments to claims 1, and 30-34 filed August 22, 2005 contain new matter. The clause in the last three line of claim 1 and lines 8 and 9 of claim 30 does not appear any where in the specification or the claims as originally filed. In fact, the various catalytic domains amino acid residues of SEQ ID NO: 22 have not been identified. Similarly, the phrases "not naturally associated thereto" in claims 30-32, "naturally received" in claim 33, and "by mutating the active site cysteine residue to a glutamine" do not appear in the specification. Applicant is required to remove the new matter from the claims. The amendment to claim 1, last three lines may use the nucleic acid fragment listed in Table 1 such as the polypeptide encoded by residues 44221 to 45243 of original SEQ ID NO: 1.

Since SEQ ID NO: 2 is a new matter, see above, claim 48 is directed to a new matter. Claims directed to a DNA sequence according to claim 1, which is nucleotide 42448-54564 of the original SEQ ID NO: 1 would obviate this rejection.

Claims 1, 4, 5, 10-12, 30-34, 37, and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 10-12, 30-34, 37, and 38 are directed to all possible DNAs encoding a monAIV polyketide synthase and the catalytic fragments thereof listed in claim 1(a)-(g) from any biological or man-made source. The specification, however, only provides a single representative species of the monAIV from *Streptomyces cinnamonenensis* encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these DNAs by any identifying structural characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Claims 4 and 5 are included with this rejection because they are directed to nucleic acid comprising a nucleic acid coding of the amino acid sequence of SEQ ID NO: 22 and a generic open reading frame from the same gene cluster.

Claims 1, 10-12, 30-34, 37, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible nucleic acid encoding monAIV from any biological source having any nucleic acid sequence and encoding any amino acid sequence comprising the activities of monAIV from *S. cinnamonenensis*. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any nucleic acid sequence encoding any amino acid sequence, said amino acid sequence comprises the

various catalytic activities of monAIV from *S. cinnamonenensis*. The specification provides guidance and examples in the form of an assay to clone the gene cluster from *S. cinnamonenensis* and identify all its opening reading frames as well as the catalytic domains found in each open reading frame (see examples, Tables 1 and 2). While molecular biological techniques and genetic manipulation to make any genetic manipulation are known in the prior art and the skill of the artisan are well developed, knowledge regarding other biological source for the nucleic acid encoding monAIV[, and all possible functional insertion, deletion, substitution and combination thereof mutants of the 4,038 is lacking. Thus, searching monAIV containing all the functional activity listed in Table 1 is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a nucleic acid encoding monAIV or any other open reading frame frame of the gene cluster is enormous. Since routine experimentation in the art does not include screening vast numbers of libraries constructed from large number of organisms and man-made mutation libraries where the expectation of obtaining the desired nucleic acid encoding monAIV or any other gene encoding any other gene of the gene cluster is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the biological source of monAIV, the amino acid required for the various catalytic activities and proper folding of the monAIV. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim 2 is objected to because it is dependent on a rejected claim. It would be allowable if rewritten in an independent form.

Claim 3 would be allowable if rewritten in an independent form and to remove the clause within a clause. For example, an isolated DNA sequence encoding monAIV of SEQ ID NO: 22.

Claim 8 would be allowable if rewritten in an independent form and remove the ambiguities in Table I by reintroducing original SEQ ID NO: 1.

Claim 48 would be allowable if rewritten in an independent form and containing all the limitation of claim 1 and relate the nucleic acid residue to those found in Table I and referring to original SEQ ID NO: 1.

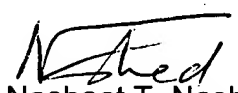
Claims directed to nucleic acid encoding functional chimeric polyketide synthase comprising one of the fragments of monAIV listed in Table I or a gene cluster comprising the entire monAIV polyketide synthase and written in a form conforming with U. S. practices and overcome the above rejections to claims 30-34, 37, and 38 would be considered favorably.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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